REMARKS

Claims 1-3 are pending in this application. Claims 1 and 3 have been withdrawn from consideration. Claim 2 has been rejected. Claim 2 has been amended. Reconsideration is respectfully requested in light of the following remarks.

I. Election/Restriction

The Restriction Requirement applied to claims 1-3 placing claims 1-3 into Groups I, II and III has been deemed proper and made final. Accordingly, Applicants have canceled claims 1 and 3.

II. Abstract

The Examiner states that the application does not contain an abstract of the disclosure on a separate sheet as required under 37 CFR1.72(b). Applicants are enclosing herewith a copy of the abstract which was published on the cover page of the PCT application of which this is the U.S. National Stage application.

III. Objection to the Specification

The specification has been objected to because the claim to priority has not been included in the specification. Applicants have amended the specification to include a paragraph claiming priority. Withdrawal of this objection is respectfully requested.

The specification has also been objected to containing trademark names that have not been capitalized. Applicants have

amended the specification to correct this informality. Withdrawal of this objection is respectfully requested.

IV. Objection to Claim 2

Claim 2 has been objected to as depending from a withdrawn claim. Claim 2 has been amended to make it an independent claim. Withdrawal of this objection is respectfully requested.

V. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claim 2 has been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner suggests that the specification does not disclose a method of diagnosing Alzheimer's disease in a patient comprising detecting in the patient an agent that increases processing of APP into β-amyloid peptides. The Examiner acknowledges that the specification teaches the use of the NT2N system to study APP processing and teaches that agents which modulate APP processing by increasing or decreasing APP-β and A-β42 can be identified by determining their effect on levels of APP-β and A-β42 produced by β- and γ-secretases in the endoplasmic reticulum of neuronal cells. Applicants respectfully traverse this rejection.

Applicants have amended claim 2 to recite that the present invention is a method diagnosing Alzheimer's disease in a patient which comprises detecting increased processing of amyloid precursor protein in neuronal cells isolated from a patient wherein the increased processing of amyloid precursor protein into amyloid β peptides is detected as an increase in the level of amyloid-β_{42} in the neuronal cells. Support for this amendment to the claims can be found throughout the specification as filed, in particular at page 13, lines 4-21 where it is discussed that increased levels of amyloid-β_{42} in neuronal cells is indicative of Alzheimer's disease lesions. Accordingly, the claim as amended is enabled by the teachings of the specification as filed. Withdrawal of this rejection is therefore respectfully requested.

VI. Rejection of Claims Under 35 U.S.C. 112, Second Paragraph

Claim 2 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner suggests that the claim does not have a step that relates back to the preamble. Applicants have amended claim 2. Therefore, withdrawal of this rejection is respectfully requested.

VII. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

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Date: **November 16, 2001**

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 1 of page 15 has been amended as follows:

Example 2 Metabolic Labeling, Gel Electrophoresis, Immunoblotting and Quantitation

Cultured NT2N neurons were starved in methionine-free DMEM HG (Life Technologies, Inc., Gaithersburg, MD) for 30 minutes prior to incubation in fresh methionine-free DMEM HG containing 0.5 mCi/ml of [^{35}S]methionine (sp act. 1000 Ci/mmol; NEN-DuPont, Boston, MA). For steady-state labeling studies, NT2N neurons were labeled with [^{35}S]methionine continuously for 16 hours. For pulse-chase studies, cells were labeled with [^{35}S]methionine for 1 hour, washed twice with methionine-containing DMEM, and then chased in the same medium for 0 to 24 hours. APP_{FL}, APPα and APPβ were separated on 7.5% Laemmli SDS-PAGE gels, and Aβ and p3 were separated on 10/16.5% step-gradient Tris-Tricine gels. These gels were either stained with Coomassie Brilliant Blue R (Pierce, Rockford, IL) and dried or transferred to nitrocellulose membranes and dried prior to exposure on PhosphorImager plates (Molecular Dynamics Inc., Sunnyvale, CA) for 3-5 days. The nitrocellulose replicas containing the

immunoprecipitates were further probed with different antibodies in accordance with procedures described by Wertkin et al. 1993 *Proc. Natl. Acad. Sci. USA* 90:9513-9517. Quantitation of bands in the autoradiogram was performed using the ~~ImageQuant~~ IMAGEQUANT software (Molecular Dynamics Inc. Sunnyvale, CA) in accordance with procedures described by Turner et al. 1996 *J. Biol. Chem.* 271:8966-8970. Radiolabeled proteins in SDS-PAGE gels and nitrocellulose replicas were also analyzed by standard autoradiographic methods. All experiments were repeated between 3 and 6 times.

Paragraph beginning at line 29 of page 15 has been amended as follows:

Example 3 Sample Preparation and Serial Immunoprecipitations

Cell lysates were prepared in accordance with procedures described by Golde et al. 1992 *Science* 255:728-730. Protein concentration was determined by the bicinchoninic acid procedure (Pierce, Rockford, IL). Media were centrifuged at 100,000 x g for one hour at 4°C before immunoprecipitation. Both cell lysates and media were precleared with protein ~~A-Sepharose~~ A-SEPHAROSE (Pharmacia Biotech, Piscataway, NJ) in RIPA for one hour at 4°C. After recentrifugation at 15,000 x g for one minute, the supernatants were rocked overnight at 4°C with fresh protein ~~A-~~

~~Sepharose~~ A-SEPHAROSE and the appropriate primary antibody. After collecting the immunoprecipitates by recentrifugation at 15,000 x g for 1 minute, the supernatants were used in a second round of immunoprecipitation with fresh protein ~~A-Sepharose~~ A-SEPHAROSE and a different primary antibody.

In the Claims:

Claims 1 and 3 have been canceled.

Claim 2 has been amended as follows:

2. (amended) A method of diagnosing Alzheimer's disease in a patient comprising detecting in the patient ~~an agent identified to~~ an increased processing of amyloid precursor protein in neuronal cells isolated from said patient ~~into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in brains of patients with Alzheimer's disease in accordance with the method of claim 1~~ wherein the increased processing of amyloid precursor protein into amyloid β peptides is detected as an increase in the level of amyloid-β_{42} in said neuronal cells , and said increase in amyloid processing is indicative of the pathogenesis of Alzheimer's disease.